REMARKS

Claims 1-13 and 25-34 are currently under consideration. Solely to facilitate prosecution, Applicants have amended claims 1 and 34 to clarify the invention. As these amendments merely change the format of these claims without changing their substance, they do not introduce any new matter. Applicants thank the Office for withdrawing its rejection of claims 1-4, 8, 9, 25, 26, and 33 under 35 U.S.C. §102(e) as allegedly anticipated by Winter et al. (U.S. Patent 6,248,516; "Winter"). Applicants respond below to each of the remaining rejections according to their statutory origin.

Rejections Under 35 U.S.C. §112

Claim 5 remains rejected under 35 U.S.C. §112, first paragraph, as allegedly not enabled. According to the Office, it is not clear that the L6 monoclonal antibody ("MAb") was publicly available. Applicants previously cited two articles by Hellström et al., one of which was published in the Proceedings of the National Academy of Sciences ("PNAS"), to demonstrate that the L6 MAb was publicly available. In the amendment filed March 7, 2003, Applicants provided a copy of the journal's author instructions from a 1997 issue of PNAS which required authors to make unique reagents publicly available as of the filing date. The Office now contends that the PNAS instructions to authors dated 1997 is not sufficient, as the effective U.S. filing date if the instant application is September 30, 1993.

Applicants submit herewith a copy of the PNAS instructions to authors for 1986, the same year the Helstrom et al. article was submitted for publication. This submission predates the instant application's effective U.S. filing date and reflects the journal policies that authors had to follow when submitting manuscripts for consideration.

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Consistent with the journal's policy in 1997, PNAS also required that any "unique materials such as antibodies . . . be available to all qualified investigators." See General Policies section, third paragraph. Thus, Applicants continue to assert that the L6 MAb was publicly available at the time of filling. Applicants request that the Office withdraw its rejection.

The Office rejects claims 1-13 and 25-34 under 35 U.S.C. § 112, first paragraph, because claims 1 and 34 allegedly contain new matter. According to the Office, part C of these claims is not discussed in the specification as being an essential element of the invention. The Office believes that the concept of partially overlapping PCR primers connecting two variable domains is only described in Example 2, without providing a generic description of this concept. Applicants respectfully traverse.

The specification provides a description of an antigen binding region's structure. Specifically, an antigen binding region "contains at least two variable domains of an antibody, preferably one variable domain or a heavy antibody chain and one variable domain of a light antibody chain (sFv fragment)." Specification, page 2, last paragraph. Thus, the specification generally refers to an sFv fragment as one possible embodiment of an antigen binding region. Example 2, which uses partially overlapping PCR primers of the type recited in claims 1 and 34, clearly explains that these primers were used to generate an sFv fragment by linking the variable domains. See specification at page 11, first paragraph. Applicants assert that the skilled artisan would understand, based upon the specification's teaching, that using partially overlapping PCR primers to link the variable domains may be generally applied to constructing antigen binding regions.

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Moreover, it is the Office's burden to demonstrate that the specification does not meet the written requirement. Applicants respectfully contend that the Office has applied the incorrect standard for the written description requirement in stating that the specification must describe a claim element as an essential aspect of the invention. Rather, Applicants have met the written description requirement when the specification can "convey clearly to those skilled in the art that the applicant has invented the subject matter later claimed." *See, e.g., In re Wertheim*, 541 F.2d 257, 262 (C.C.P.A. 1976). As discussed above Applicants have met the written description requirement with respect to this claim element. Applicants request that this rejection be withdrawn.

Claims 1-13 and 25-34 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. The Office believes that the format of claims 1 and 34 is improper because these claims recite a compound and part C, which describes a method step, is not a distinct element of the compound. Solely to facilitate prosecution and without prejudice or disclaimer, Applicants have amended claims 1 and 34 to clarify that this distinct feature, using partially overlapping PCR primers, is further descriptive of the antigen binding region recited in parts A and B of the claims. Regarding 37 C.F.R. § 1.75(i), Applicants believe that these claims are in conformance with claim format, as each step in the claims is separated by a line indentation. As this rejection has been rendered moot, Applicants request that this rejection be withdrawn.

Rejections Under 35 U.S.C. §102

The Office rejects claim 34 as allegedly anticipated Under 35 U.S.C. §102(a) by Bagshawe (WO 93/13805). According to the Office, Bagshawe teaches constructs of an antibody binding site and a prodrug enzyme. Further, Bagshawe allegedly suggests

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that the antigen binding site can be an sFv fragment containing an oligopeptide linking the variable domains and that the antigen binding site can be chemically linked to the enzyme. Finally, the Office believes that only the teaching of a oligopeptide linker is needed to anticipate part C of the claim. Bagshawe does not anticipate claim 34 for the following reasons.

First, the invention of claim 34 uses an antigen binding site to target an enzyme to diseased cells. This enzyme activates an inactive prodrug so that the resulting activated drug will destroy the diseased cell. Bagshawe's enzymes do not activate a prodrug. Rather, these enzymes inactivate a compound (A) that in turn inactivates a cytotoxic compound (B). As described in Bagshawe at page 22, lines 1-7, the skilled artisan administers compound A and compound B in such a way as to allow compound A to protect normal cells from compound B's activity. Pre-administration of the enzyme conjugate targets diseased cells so that when the protective compound A is present, the enzyme destroys the protective activity and allows cytotoxic compound B to kill the diseased cell. For example, Bagshawe's Example 1 discusses the use of folinic acid (compound A) and trimetrexate (compound B). As such, the reagents used in Bagshawe's system are different in that compound A and compound B do not function as prodrugs. Thus, Bagshawe's invention does not relate to activating a dormant prodrug.

Second, claim 34 requires that the antigen binding regions consist of a single polypeptide chain. Though Bagshawe may generally mention sFv fragments as a type of antigen binding domain, this general discussion of sFv fragments by no means enables a skilled artisan to design a compound in which an sFv fragment is linked to an

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enzyme. The Bird et al. and Huston et al. references cited at page 6 of Bagshawe describe only the production of sFv fragments and not how to use them in any other molecular context. Moreover, Bagshawe's examples teach a chemical conjugation of an enzyme to $F(ab)_2$ antibody fragments. *See* Examples 6 and 7. $F(ab)_2$ fragments are not single chain antigen binding regions. Rather, the two variable regions are on separate chains.

Finally, the Office has again dismissed the importance of Applicants' use of overlapping PCR primers to generate the linker between the variable domains in the single chain antigen binding region. Though Bagshawe briefly mentions PCR at page 19, lines 19-24, there is no teaching of its use to generate the single chain antigen binding region itself. Applicants continue to assert that the description of the polypeptide linker as provided in part b) of amended claims 1 and 34 should not be dismissed. As previously discussed, the Federal Circuit has indicated that this type of description should not be ignored when construing the claim's meaning. *See Atlantic Thermoplastics Co. v. Faytex Corp.*, 970 F.2d 834, 23 U.S.P.Q.2d 1482 (Fed. Cir. 1992). Moreover, in Applicants' prior response when addressing a rejection under 35 U.S.C. § 102(e) based on Winter et al. (U.S. Patent 6,248,516; "Winter") Applicants noted that Winter did not teach a linker generated during a PCR step. In the current Office Action, the Office has not maintained this rejection presumably in light of Applicants' arguments. The Office has not employed consistent standards when rejecting the pending claims. Applicants therefore request that this rejection be withdrawn.

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Claim 34 stands rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Hellstrom et al. (U.S. Patent 5,869,045; "Hellstrom"). The Office believes that Hellstrom teaches that an sFv can be constructed with a peptide bridge between the variable domains and that the sFv was formed by a PCR reaction. Applicants traverse.

The Office's interpretation of Hellstrom is inaccurate. Though Hellstrom used PCR to generate a single chain construct, the linker connecting the variable domains was not formed during the PCR reaction, as required by step b) in amended claim 34. As described at column 74, lines 23-27 and at column 75, lines 36-48, Helstrom amplified a DNA sequence from the pBR96Fv plasmid, which already contained the V_L-linker-V_H sequence. The primers used to amplify that 550 bp were located in the variable domains and not in the linker. Figure 36 diagrams how the 550 bp NdeI/KpnI fragment was produced. Thus, Hellstrom did not prepare an sFv fragment by using PCR primers that formed the linker during the PCR reaction. Applicants request that the Office withdraw its rejection, as this reference cannot anticipate claim 34.

Claim 34 stands rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Borstel et al. (U.S. Patent 6,258,360; "Borstel"). Borstel allegedly describes fusion proteins that contain a single chain antibody and an enzyme that activates a prodrug. The Office further notes that Borstel's constructs contain a polypeptide linker sequence. Claim 34 is not anticipated by Borstel for the following reason.

Even if Borstel generally describes a linker sequence between two variable domains in a single chain construct, this reference does not teach the use of PCR primers to form the linker during a PCR reaction, as required by claim 34. As discussed throughout this response, this aspect of the claimed invention provides a meaningful

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description of the resulting linker and reflects part of the inventors' contribution to the art. As Borstel does not teach all of the elements of claim 34, Applicants respectfully request that this rejection be withdrawn.

Rejections Under 35 U.S.C. §103

The Office continues to reject the pending claims under § 103(a) in two general groups: one in which Bosslet et al. (*Brit. J. Can.* 65:235 (1992); "Bosslet"); Seemann et al. (Canadian Patent 2,062,047; "Seemann"); and Eaton et al. (EP 392,745; "Eaton") are the primary references and a second in which Winter is the primary reference. Applicants address these rejections according to their groups below.

Rejections based on Bosslet, Seemann, Eaton, Huston, and Bosslet 2

Claims 1-9, 25-27, 30, 33, and 34 are rejected under 35 U.S.C. §103(a) as allegedly obvious over Bosslet or Seemann or Eaton in view of Huston et al. (U.S. Pat. 5,258,498; "Huston") and Bosslet et al. (U.S. Pat. 5,591,828; "Bosslet 2"). According to the Office, Bosslet and Seemann both teach a fusion protein comprising a Fab, a linker, and a human β-glucuronidase. The Office also alleges that Eaton teaches a fusion protein comprising a Fab and an *E. coli* β-lactamase.

Applicants acknowledge that the Office has applied a different Huston reference as compared to the previous Office Action. According to the Office, Huston teaches that antigen binding regions are formed by joining a V_H and a V_L domain via a spacer and that such antigen binding regions may be present in one or more copies. Huston also allegedly teaches that these antigen binding regions may be fused to other molecules such as enzymes. Finally, the Office believes that Huston teaches a linker with an amino acid sequence (GlyGlyGlyGlySer) 3. The Office also relies on Huston for the

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proposition that expression of these proteins in eukaryotic cells would lead to protein glycosylation.

The Office combines these references, asserting that it would have been obvious to modify the Fab fusion protein constructs of Bosslet, Seemann or Eaton by substituting the single chain antigen binding regions allegedly taught by Huston. In making its rejection, the Office provides several observations that it believes constitute motivations for making the asserted combination. First, the Office contends that because Huston teaches that antigen binding regions may be fused to enzymes, a skilled artisan would have expected that glucuronidase would be useable with Huston's antigen binding regions. Applicants note that the Office makes a conclusion without providing any support in the cited references. In essence, this alleged motivation is based on the Office's general knowledge about the art. As Applicants explained in the previous response, reliance on well known scientific knowledge or common knowledge to provide motivation is directly contrary to the Federal Circuit's decision in *In re Lee*, 277 F.3d 1338 (Fed. Cir. 2002). The Office is required to provide an evidentiary basis for its conclusory statements.

Second, the Office believes that the skilled artisan would have recognized that Fab, Fv, and sFv constructs are functionally equivalent. Whether these constructs are functionally equivalent or not is not relevant to the pending claims, which describe the claimed compound according to its structure. And, *arguendo*, even if an Fab fragment and an sFv fragment were functionally equivalent, they are by no means structurally equivalent, a fact to which the Office has agreed. *See* Office Action of June 7, 2001, Paper 20, p. 4, line 20 to p. 5, line 3. As the Office has not addressed this issue,

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Applicants continue to assert that the Office is making an incorrect comparison when attempting to base its obviousness rejection on alleged functional equivalents.

Third, the Office refers to several alleged benefits to single chain constructs as discussed by Huston. Even if these benefits were true, a skilled artisan would not necessarily be motivated to produce a single chain construct in the absence of a showing that both the antigen binding region and the biologically active portion of the fusion protein retained their respective functions. Indeed, Huston merely suggests that an enzyme could be attached to a single chain antigen binding region. In Huston's example, a single chain antigen binding region was attached to the FB fragment of Protein A. See cols. 27 and 28. Protein A is not an enzyme, but a protein known to bind IgG. Though Huston verified that the Protein A portion of their fusion protein bound IgG, this does not provide a reasonable expectation of success to the skilled artisan with respect to enzymes, the activity of which may be more sensitive to changes in protein folding that occur with single chain constructs.

Neither Bosslet, Seemann, nor Eaton address this issue because they all employ Fab fragments, as acknowledged by the Office. In addition, Bosslet 2 does not use single chain antigen binding regions. Rather, this reference uses a linker to fuse together two different immunoglobulin heavy chains. The resulting construct is introduced along with a construct encoding the immunoglobulin light chain to produce a Fab with two different specificities. Thus, Bosslet 2 does not teach a single chain antigen binding region. In sum, all of the references cited by the Office, except for Huston, do not use a single chain antigen binding region and cannot convey a reasonable expectation of success for any construct expressing a single chain antigen

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binding region. Though Huston may discuss these types of antigen binding regions and a general suggestion that these regions may be coupled to enzymes, there is no showing that such a construct would retain both binding activity and enzymatic activity.

Fourth, the Office independently concludes that there is an inherent advantage to using single chain constructs. Applicants note that the citations given by the Office only support the notion that Huston transformed bacteria with a single DNA construct while Bosslet transfected BHK cells with two DNA constructs. These citations do not support the Office's assertion that there are inherent benefits to single chain constructs. In addition, the Office suggests that a skilled artisan would expect to be able to develop bivalent or multivalent single chain construct without significantly increasing the size of the resulting fusion protein. In making this statement, the Office did not provide any supporting citation and again, is importing its general knowledge of the art to provide a source of motivation, counter to the Federal Circuit's reasoning in *Lee*.

Finally, the Office believes that Huston provides motivation for producing the claimed invention by generally discussing that a bivalent or multivalent construct may have high affinity for the target antigen. Even if this were true, as discussed above, none of the references cited provide a reasonable expectation of success in making a monovalent construct with an enzyme let alone an multivalent construct.

As discussed above, the description of the polypeptide linker as provided in part b) of amended claims 1 and 34 should not be overlooked. The Office continues to consider the compound of claims 1 and 34 without acknowledging how the linker is formed in step b). Bosslet, Seemann, Eaton, and Bosslet 2 do not teach single chain constructs. Huston, though the reference discusses single chain constructs, does not

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suggest that the linker be formed as set forth in claims 1 and 34. Thus, none of the references cited by the Office teach the concept of variable domains linked by a polypeptide linker that is ultimately produced by overlapping PCR primers. As such, they cannot make independent claims 1 and 34 obvious or their dependent claims obvious. For the reasons stated above, Applicants respectfully request that the Office withdraw its rejection of claims 1-9, 25-27, 30, 33, and 34.

Claims 1, 11, 12, 31, and 32 are rejected as allegedly obvious over Bosslet or Seemann or Eaton in view of Huston and Bosslet 2 and in further view of Ong et al. (*Can. Res.* 51:619 (1991); "Ong") and Bagshawe et al. (WO 89/10140; "Bagshawe"). According to the Office, Huston teaches that polypeptides containing sFv may be produced in Gram-negative bacteria, such as *E. coli*. The Office then independently asserts that the protein will be correctly folded when expressed these bacteria. The Office concludes that one would have been motivated to use *E. coli* to produce correctly folded proteins in large amounts. Ong allegedly teaches that it is advantageous to glycosylate antibodies to permit rapid clearance. The Office also relies on Bagshawe for a similar teaching. The Office then concludes that because antibody-enzyme conjugates are functionally equivalent to sFv-enzyme proteins, it would be obvious to glycosylate sFv-enzyme fusion proteins.

The Office has indicated that Applicants' previous discussion of Ong and Bagshawe were improper because they were made in isolation from the other cited references. Applicants note, however, that before a conclusion may be reached as to the total teaching of all the cited references, each reference must be assessed for the contribution it makes. As previously noted, Ong does not teach antibody-enzyme

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conjugates. Second, antibodies conjugated to galactose are not functionally equivalent to an sFv fragment linked to a pro-drug activating enzyme, as Ong's constructs do not contain enzymes. Third, *arguendo*, even if they were functionally equivalent, this is not the appropriate comparison to make. The compound of claim 1 is defined by its structure, not function. Ong does not contemplate the structure described in claim 1 and there is no way to know from Ong's teaching whether glycosylation would work with the structure described in claim 1. Such uncertainty is manifest in the fact that Ong tested the other biological functions of the galactose-conjugated antibodies (i.e., complement-mediated cytotoxicity and cell-mediated cytotoxicity) to be sure that galactose conjugation did not affect these functions. *See* Ong at p. 1620, right column. The inventors of the claimed invention, however, have shown that glycosylation is in fact possible with the compound of claim 1. Bagshawe conjugates enzymes to whole antibodies or to Fab fragments (see p. 20), but does not teach conjugating an enzyme to an sFv fragment, which is a different structure.

The Office currently notes that Huston teaches that sFv constructs are desirable alternatives to antibodies and Fabs. Applicants note, however, that Huston does not discuss the impact of glycosylation on single chain constructs. Thus, none of the references cited provide a motivation to glycosylate the compound of claim 1. Moreover, Ong and Bagshawe do not compensate for the lack of teaching that a peptide sequence linking two variable domains is formed during PCR. Claims 1, 11, 12, 31, and 32 cannot be obvious in light of these references. Applicants respectfully request that the Office withdraw this rejection.

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The Office maintains its rejection of claims 1, 10, 13, and 29 under 35 U.S.C. §103(a) as allegedly obvious over Bosslet or Seemann or Eaton in view of Huston, Bosslet 2, Bagshawe, Ong, and in further view of Goochee et al. (*Biotechnol.* 9:1347 (1991); "Goochee"). According to the Office, Goochee shows that yeast could express a polypeptide having a high degree of mannosylation, which would facilitate rapid clearance. The Office concludes that it would have been obvious to produce a polypeptide with mannose moieties to provide rapid clearing of the polypeptide. See Office Action of June 7, 2001 at pp. 9 and 10. Applicants refer to the arguments above regarding Bosslet, Seemann, Bosslet 2, Bagshawe, and Ong, while addressing Goochee below.

Goochee provides a general discussion about oligosaccharide structures in proteins produced by mammal cells, yeast cells, insect cells, and plant cells. Though Goochee does teach that yeast express mannosylated proteins and that mannosylation proteins are rapidly cleared from the host via the liver and macrophage, there is no suggestion nor motivation to apply this to antibodies in particular let alone the sFv/enzyme complex described in claim 1. Goochee discusses antibodies only in the context of their recognizing epitopes blocked by oligosaccharides and antibodies that recognize the oligosaccharide moiety itself. A general observation that yeast can mannosylate proteins and that these proteins may be cleared from the blood quickly does not motivate one to use yeast in the specific application of expressing the sFv/enzyme complex of claim 1. As discussed above, neither Bosslet, Seemann, Bosslet 2, Bagshawe, nor Ong provide the requisite motivation, thus failing to make

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claims 1, 10, 13, and 29 obvious. Applicants therefore request that the Office withdraw its rejection.

The Office rejects of claims 1 and 28 under 35 U.S.C. §103(a) as allegedly obvious over Bosslet or Seemann in view of Huston, Bosslet 2, Eaton, and in further view of Bagshawe et al. (WO 88/07378; "Bagshawe 2"). The Office believes that Bagshawe 2 provides that it was known and conventional to provide carboxypeptidase G2 from *Pseudomonas* as a prodrug activating enzyme. Applicants refer to the arguments above regarding Bosslet, Seemann, Eaton, Huston, and Bosslet 2, while addressing Bagshawe 2 below.

Bagshawe 2 discusses antibody or antibody fragment/enzyme proteins. But antibody fragments are defined as $F(ab)_2$ or $F(ab)_1$ fragments and not sFv fragments. *See* p. 7, lines 2-6 and p. 8, lines 9-12. Thus, this reference does not provide the motivation to use carboxypeptidase G2 in concert with the structure of an sFv fragment. Further, neither Bosslet, Seemann, Eaton, Huston, nor Bosslet 2 teach carboxypeptidase G2 and fail to provide a motivation for this combination.

Moreover, none of these references teach the formation of the linker described in part b) of amended claim 1. The Office opines that because Huston allegedly teaches the same linker amino acid sequence as provided in the specification, the method by which the compound of claim 1 is made becomes irrelevant. For the reasons set forth above, the description recited in step b) should be considered. Applicants therefore request that the Office withdraw its rejection, as these references in combination do not make the invention of claims 1 and 28 obvious.

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Rejections based on Winter

The Office maintains but modifies its rejections of the pending claims under 35 U.S.C. §103(a) in view of Winter and a combination of other references. These rejections are as follows:

1. Claims 1-4, 8, 9, 25, 26, 33, and 34 are rejected as allegedly obvious in light of Winter in view of Huston. According to the Office, Winter teaches single domain ligands, including sFv fragments, that can be linked to an effector molecule such as a prodrug activating enzyme. Winter also allegedly teaches that the single domain ligands may be present in multiple copies. The Office acknowledges, however, that Winter does not clearly teach whether there is a linker between the variable domains in the sFv fragment. The Office relies on Huston to teach such a linker and more specifically, a linker with the sequence (GlyGlyGlyGlySer)3. Applicants note that the Office has applied these two references in the same manner for the additional rejections below, based on Winter.
2. Claims 1, 2, 4, 5, 7, and 9 remain rejected as allegedly obvious in light of Winter and in view of Huston and in further view of Seemann. The Office believes that Seemann teaches therapeutic fusion proteins with binding specificity to CEA and that have β-glucuronidase activity. The Office then asserts that CEA is a known tumor antigen and β-glucuronidase is a known pro-drug activating enzyme and concludes that it would have been obvious to combine these activities with Winter's single domain ligand

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constructs. The Office also asserts that expression of proteins in BHK cells would "inherently" result in glycosylation.

3. Claims 1, 6, 27, and 30 remain rejected as allegedly obvious in light of Winter in view of Huston and in further view of Eaton. Specifically, the Office contends that while Winter does not teach β-lactamase as a pro-drug activating enzyme, Eaton teaches that such enzymes were known in the art in the context of antibody conjugates. Thus, according to the Office, it would have been obvious to use this enzyme in the context of Winter's sFv compositions.
4. Claims 1, 6, and 28 remain rejected as allegedly obvious in light of Winter in view of in view of Huston and in further view of Bagshawe 2. According to the Office, Winter does not teach carboxypeptidase G2 as a prodrug activating enzyme but Bagshawe 2 demonstrates that this enzyme was a known prodrug activating enzyme. Thus, the Office believes that it would be obvious to use this enzyme in the context of Winter's single domain ligand constructs.
5. Claims 1, 2, 9, 11, 12, 31, and 32 are rejected as allegedly obvious in light of Winter in view of Huston and in further view of Ong and Bagshawe et al. (WO 89/10140; "Bagshawe 3"). Winter and Huston allegedly teach production of single chain constructs in bacteria. Ong allegedly teaches that it is advantageous to glycosylate antibodies to permit rapid clearance. The Office also relies on Bagshawe 3 for teaching the desirability of glycosylating antibody/prodrug activating enzyme conjugates. The Office

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concludes that because antibody/enzyme conjugates are functionally equivalent to sFv/enzyme fusion proteins, it would be obvious to glycosylate and mannosylate sFv/enzyme fusion proteins.

6. Claims 1, 10, 13, and 29 remain rejected as allegedly obvious in light of Winter in view of Huston, Ong, Bagshawe 3 and in further view of Goochee. The Office uses Ong and Bagshawe 3 as described above for claims 1, 2, 9, 11, 12, 31, and 32. The Office believes that, because Goochee allegedly shows that yeast can express mannosylated proteins that are rapidly cleared, it would be obvious to express the polypeptide of claim 1 in yeast to attain mannosylation and rapid clearance. The Office also asserts that Goochee particularly teaches the proteins of claims 10 and 13 and that, even though claim 29 is not covered, the skilled artisan would have been able to determine which yeast strains would have been appropriate.

Applicants note that in maintaining these rejections based on Winter, the Office continues to ignore the process step as recited in step b) of amended claims 1 and 34. This process step provides a meaningful description of the polypeptide linker and as such should not be dismissed. To construe the pending compound claims without regard to the process step ignores the Applicants' inventive step in producing the claimed compound by linker formation during the PCR reaction. As discussed above, the Federal Circuit in *Atlantic Thermoplastics* has agreed with this claim interpretation. Applicants assert that none of the references cited by the Office teach the concept of variable domains linked by a polypeptide linker that is produced by

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overlapping PCR primers. As such, they cannot make independent claims 1 and 34 obvious or their dependent claims obvious. Applicants therefore respectfully request that the Office withdraw these rejections based on Winter.

Conclusions

In view of the foregoing amendments and remarks, Applicants respectfully request the reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

Dated: July 22, 2003

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